Avram Goldstein, M.D.
Professor Emeritus of Pharmacology, Stanford University
735 Dolores, Stanford, CA 94305-8427
650-324-9251 (FAX 650-328-8412)
e-mail: avram.goldstein@stanford.edu

September 22, 1999

Jane E Henney, MD, Commissioner
Food & Drug Administration
Parklawn Bldg Rm 14-71
5600 Fishers Lane
ROCKVILLE MD 20857

cc: Virginia L. Wilkening, Acting Director, Office of Food Labeling; Joseph Levitt, Director, Center for Food Safety & Applied Nutrition; William Hubbard, Associate Commissioner, Office of Policy Coordination.

Re: Docket No. 97P-0498/CP1

Dear Dr. Henney:

I am writing to you at the suggestion of my old friend and colleague Elkan Blout, who thinks you would be interested in the scientific issue here concerning caffeine.

More than two years ago, on July 7, 1997, a petition was filed with FDA, initiated by Professors John Hughes (University of Vermont), Roland Griffiths (Johns Hopkins) and me (Stanford), and co-signed by 21 other academician experts, requesting that the amount of caffeine (in excess of 5 mg per serving) in foods or beverages be stated on the label.

This petition was submitted simultaneously with one from the *Center for Science in the Public Interest* requesting the same action.

Both petitions are appended to this letter as *Attachments 1 and 2*, and the chronological history of our thus-far unsatisfactory dealings with FDA is appended as *Attachment 3*.

My personal research interest in caffeine dates back 35 years to my conduct of the very first double-blind rigorously controlled clinical trials with this drug (1,2). And as recently as two years ago, I conducted a survey of caffeine consumption and its effects in school children (3). (These references, cited below, were not included among those submitted with our petition.)

All studies of caffeine have shown it to be an addictive psychostimulant with adverse dose-related health effects in users. Chronic high dosage leads to dependence, as has

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been shown repeatedly by a withdrawal syndrome (recognized in DSM-IV), which is characterized by headache, fatigue, dysphoria, and cognitive and somatic disturbances. Caffeine is added to soft drinks; and children may consume very large daily amounts -- sometimes the equivalent of several cups of coffee for an adult.

We do not see anything complex about our request that the amount per serving be disclosed on the label. We believe that parents have a right to know how much their children are consuming. Present labeling regulations require only that the presence of added caffeine, but not its amount, be stated.

We would very much appreciate your taking a personal interest in this. At the least, we would like to be told what the so-called "complex issues" are (see *Attachment 3*). Then we and FDA might be able -- in a spirit of cooperation -- to resolve them in the interest of the public. We urge FDA to include caffeine labeling as a high priority issue for the coming year.

References not included in petition:

(1) A Goldstein: Arch Exp Pathol Pharmakol, 248,269-278,1964.

(2) A Goldstein et al: J Pharmacol Exper Ther 149,156-159;150,146-151,1965; Clin Pharmacol Ther 10,477-488;489-497,1969.

(3) A Goldstein & ME Wallace: Exper Clin Psychopharmacol 5,388-392,1997.

A GOLDSTEIN to JE HENNEY
Attachment 1

y of Vermont

:HAVIORAL PHARMACOLOGY LABORATORY
DEPARTMENT OF PSYCHIATRY
38 FLETCHER PLACE — IRA ALLEN SCHOOL
BURLINGTON, VERMONT 05401-1419
TELEPHONE: (802) 660-3060
FAX: 802-660-3064

July 7, 1997

Michael Friedman, MD
Lead Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane, Room 1471
Rockville MD 20857

Dear Dr. Friedman,

We are scientists who have extensively researched the behavioral effects of caffeine. We are writing to petition the FDA to include information on caffeine content in the labeling of foods and beverages. Our petition is based on recent evidence of the adverse behavioral effects of caffeine including the possibility of dependence.

Specifically, we recommend that all foods and beverages (including coffees, teas and sodas) which contain more than 5 mg of caffeine per serving include a statement of the mg of caffeine per serving.

The rationale for this recommendation is threefold: 1) caffeine can and does produce behavioral problems in adults and children, 2) caffeine use is ubiquitous, and 3) many consumers wish to know caffeine levels.

Behavioral Harm From Caffeine

Recent evidence has confirmed clinical observations that caffeine can induce anxiety, insomnia, intoxication (restlessness, difficulty concentrating, etc) and withdrawal (headaches, drowsiness, fatigue, etc.) (1,2). In fact, in some individuals, anxiety can occur with use of as little as 250 mg of caffeine (3) and withdrawal with as little as 100 mg/day (4). That caffeine can induce these problems is based on multiple well-controlled scientific studies (5,6). For example, caffeine can induce true panic attacks requiring medical treatment in susceptible individuals (6). The evidence of behavioral harm is sufficient such that it is recognized by the American Psychiatric Association in its DSM-IV official nomenclature (7) and in almost all standard medical textbooks.

Behavioral problems from caffeine are not rare. In one population-based study of adults (8), 30% of users reported caffeine-induced anxiety in the last year and 39% reported caffeine-induced insomnia. Of those who stopped caffeine use, 24% reported meeting the full DSM-IV criteria for a withdrawal syndrome.

Behavioral problems from caffeine are not confined to adults. Several experimental studies have demonstrated that some doses of caffeine can cause anxiety and restlessness in children (9). In addition, caffeine may have dependence potential in children (10,11). In one study, several children repeatedly chose caffeinated sodas in preference to uncaffeinated sodas in double-blind tests (11). The caffeinated and noncaffeinated sodas did not differ in taste tests; thus, it is clear these children were using the sodas for the pharmacological effects of caffeine. In another study, when 6-12 year old children abruptly stopped caffeine, their ability to attend to a task worsened and they developed headaches (10).

Prevalence of Caffeine Use

Caffeine is the most widely used psychoactive drug in the U.S. (12). It is also the only pharmacologically active and psychoactive substance permitted to be added to foods and beverages. The usual dose of caffeine from brewed coffee is approximately 100 mg/6 oz serving, from tea is 40 mg/6 oz serving and from soda is 40 mg/12 oz serving (12).

In the most recent surveys (12,13), 83% of adults report currently using caffeine with a mean intake of 200-250 mg/day among users. Among children, in the last nationwide survey (14), 98% consumed caffeine in the last week. The mean caffeine intake among children is low (1.0 mg/kg/day compared to 3.0 mg/kg/day in adults); however, there are some children with relatively high intakes (12). Coffee remains the greatest contributor of caffeine intake in adults (12); however, there has been a dramatic increase in caffeinated soda use in adults the last 20 years (15). Sodas are the major source of caffeine for children (15)

It is important to recognize the ubiquity of caffeine use for two reasons. First, the widespread use of caffeine makes it similar to protein, fat, cholesterol, carbohydrates and other currently labeled food ingredients in that it is consumed daily by almost the entire population. Second, the public health importance of exposure to a substance is the product of its impact and its degree of exposure. Thus, for example, a caffeine-induced problem that occurs in only 5% of users will still affect some 10 million consumers (1).

Public Interest in Caffeine Contents

The public's interest in the caffeine content of beverages and foods has increased substantially in the last decade. This is best illustrated by substantial sales of decaffeinated coffees and teas and noncaffeinated sodas; e.g., about 15% of coffee (12) and 30% of soda sales (Adamson, D., personal communication, 1995) are noncaffeinated. In addition, several "lite" coffees with "half" the usual caffeine content have been marketed without actual statements of caffeine amounts. Finally, new clear caffeinated waters can easily be mistaken for being caffeine-free. In summary, the market is changing such that simply listing the presence/absence of caffeine in fine print in a list of many other ingredients is insufficient. It is ironic that many consumers are choosing foods based on caffeine content but cannot discern how much caffeine is in them whereas consumers rarely choose foods based on their vitamin content but can find their vitamin contents on every food.

Our Recommendation

We are suggesting 5 mg per serving as the dose of caffeine in a food at which labeling should occur. Recent evidence indicates doses as low as 10 mg can produce mood changes that are discriminated by humans (16) and doses as low as 25 mg can induce caffeine self-administration (17); i.e., use of a beverage for the effect of caffeine. Thus, repeated doses of 5 mg could produce pharmacological effects. Although serving sizes vary across foods and beverages, we would note that although the industry has used 5 oz as a serving size for caffeinated beverages, 7-8 oz is a much more common serving size (12).

Summary

In summary, we believe the well-accepted evidence that caffeine can cause behavioral harm, the widespread use of caffeine, and the public's interest in knowing the caffeine content of their foods are compelling arguments that FDA should provide consumers with the caffeine content of all caffeine-containing foods and beverages.

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John R. Hughes, M.D.
Professor, Dept of Psychiatry
Dept. of Psychiatry
University of Vermont

Roland R. Griffiths, Ph.D.
Professor
Depts. of Psych and Neuroscience
Johns Hopkins University

Avram Goldstein, M.D.
Professor Emeritus
Dept. of Pharmacology
Stanford University

Enclosed are signatures of other scientists who agree with our petition.

If you have questions about this proposal, please contact John R. Hughes, M.D. via phone: (802)660-3065; Fax: (802)660-3064, email: john.hughes@uvm.edu or mail: Human Behavioral Pharmacology Lab, University of Vermont, 38 Fletcher Place, Burlington, Vermont 05401-1419.

We understand the Center for Science in the Public Interest will also be sending a petition on caffeine to you in the next few weeks. We would like our petition to be considered along with this. We would appreciate a written response to our proposal to be forwarded to Dr. Hughes after receipt of the CSPI paper.

Name	Title	Department	Affiliation	City	State	Fax Number
Neal Benowitz, Ph.D.	Professor	Psychiatry	San Francisco General Hospital	San Francisco	CA	4152064956
Gail Bernstein, M.D.	Associate Professor	Psychiatry	University of Minnesota Med School	Minneapolis	MN	6126265591
Marilyn Carroll, Ph.D.	Professor	Psychiatry	University of Minnesota	Minneapolis	MN	6126248935
Suzette Evans, Ph.D.	Assistant Professor	Psychiatry	NY State Psychiatric Institute	New York	NY	2127958860
Jack E. Henningfield, Ph.D.	Professor		Pinney Associates, Inc.	Bethesda	MD	3017180034
Frank Holloway, Ph.D.	Professor	Psychiatry & Behavioral Science	Univer of Oklahoma Hlth Sciences Ctr	Oklahoma City	OK	4052712356
Steve Holtzman, Ph.D.	Professor	Pharmacology	Emory University School of Medicine	Atlanta	GA	4047270365
Leonard Howell, Ph.D.	Research Scientist	Pharmacology	Emory University School of Medicine	Atlanta	GA	4047271266
Jack James, Ph.D.	Professor	Psychology	LaTrobe University	Australia		01161394791783
Lynn T. Kozlowski, Ph.D.	Professor	Behavioral Health	Pennsylvania State University	University Park	PA	8148637525
James D. Lane, Ph.D.	Associate Research Professor	Psychiatry & Behavioral Health	Duke University Medical Center	Durham	NC	9196848629
Anthony Liguori, Ph.D.	Assistant Professor	Physiology & Pharmacology	Bowman Gray School of Medicine	Winston-Salem	NC	9107168501
Alison Oliveto, Ph.D.	Assistant Professor	Psychiatry	VA Medical Center	West Haven	CT	2039373478
John D. Roache, Ph.D.	Associate Professor	Psychiatry	Psychiatry Mental Science	Houston	TX	7137941425
Jed E. Rose, Ph.D.	Chief	Nicotine Research Lab	Veterans Administration Medical Ctr	Durham	NC	9192861388
Craig Rush, Ph.D.	Assistant Professor	Psychiatry & Human Behavior	University of Mississippi Medical Ctr	Jackson	MS	6019845885
Kenneth Silverman, Ph.D.	Assistant Professor	Psychiatry & Human Behavior	Johns Hopkins University	Baltimore	MD	4105501483
Roger D. Spealman, Ph.D.	Professor	Behavioral Biology	NE Regional Primate Research Ctr	Southborough	MA	5086248197
Eric Strain, M.D.	Assistant Professor	Behavioral Pharmacology	Biobehavioral Biology Research Ctr	Baltimore	MD	4105500030
Thomas W. Uhde, M.D.	Professor	Psychiatry	Wayne State University	Detroit	MI	3135775900
Philip Woodson, Ph.D.	Doctor of Natural Science		Intelligentsia, Inc.	Upper Montclair	NJ	2017468322

July, 1997

Lead Deputy Commissioner Michael Friedman, M.D.
5600 Fishers Lane
Room 1471
Rockville, MD 20857

Dear Dr. Friedman:

In 1981, the Food and Drug Administration (FDA) began advising pregnant women to "avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly."[1] We compliment FDA for continuing that advisory to pregnant women. Since 1981, a growing body of evidence suggests that caffeine consumption by women who are pregnant or might become pregnant increases the risk of delayed conception,[2-6] fetal growth retardation,[7-13] and miscarriage.[14-16]

In addition to the effects on reproduction, caffeine has been shown to affect calcium balance and may contribute to decreased bone density and osteoporosis.[17-21] While the effect of caffeine on calcium balance may be modest, the impact on the public's health could be significant because many American women consume inadequate amounts of calcium.

Caffeine also can cause behavioral effects, including anxiety, sleeplessness, addiction, and withdrawal upon cessation of consumption.[22-25] Those behavioral effects have been reported in children as well as in adults.[26-28]

In addition, many children consume large quantities of (and may be addicted to) soft drinks and other caffeinated beverages, which are often high in calories and devoid of nutrients, in place of more nutrient-dense beverages such as fruit juice and milk. 1994 USDA data show that teenagers drink more soft drinks than milk.[29] They also show that children under 5 years drank 16% less milk than in the late 1970s and 23% more soft drinks.[30] In another study, children who consumed one or more soft drinks a day consumed one-fifth less calcium than children who did not drink soft drinks.[31]

To give consumers more information to make educated decisions about caffeine consumption, we urge that the FDA implement the following measures.

I. The Food and Drug Administration should require that caffeine content be disclosed on food labels.

Caffeine is present in a variety of foods and beverages. It is found not only in coffee, tea, and colas but also in other soft drinks, caffeinated water, ice cream, and yogurt. It is difficult for consumers to predict the caffeine content of many of those foods and beverages, since many of the products are new and the levels of caffeine vary widely between brands. For example, caffeinated bottled waters, marketed only since 1995, contain anywhere from 50-125 mg of caffeine per half-liter bottle. Also, coffee-flavored products such as coffee yogurt and coffee ice

cream can contain as much caffeine as cola or tea.

Many Americans are interested in information about the caffeine content of foods and beverages so that they can manage their intake. Drivers who wish to stay awake and students studying for exams may rely on caffeine to help them stay alert. The parents of young children might wish to limit their children's consumption of beverages containing this stimulant close to bedtime. Pregnant women may wish to choose products with less caffeine or entirely eliminate caffeine from their diet. Others might wish to limit their caffeine intake to help prevent side effects such as nervousness, irritability, or sleeplessness.

Thus, we urge the FDA to require that foods that contain significant amounts of caffeine (either naturally or as a food additive) disclose on the food label the amount of caffeine (in milligrams) per serving.

II. FDA should conduct a thorough review of the health effects of caffeine and determine what other actions should be taken to protect the public from any adverse effects of caffeine.

Caffeine is the only drug that is widely added to the food supply. It is consumed by a large proportion of the population. Caffeine is an addictive stimulant. Scientific research has demonstrated that caffeine consumption affects reproduction, behavior, and bone-mineral metabolism and has negative nutritional consequences for children.

The FDA should conduct a thorough review of the effects of caffeine on health and behavior to determine if further regulatory or educational actions should be taken to inform consumers about adverse effects associated with caffeine consumption.

Sincerely,

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GOLDSTEIN TO HENNEY, ATTACHMENT 3

Chronological history of the petitions and related correspondence.

October 3, 1997: Dr. Hughes (having had no response from FDA) asked about the status of our petition and enclosed an article from the *Journal of the American Dietetic Association* (February 1997, page 179) containing a table showing how widely varied is the amount of caffeine in various caffeinated soft drinks -- from 5.2 to 55.8 mg per 12-oz serving, yet the consumer has no way of knowing the amount.

November 20, 1997: A small revision to our petition was submitted, setting a threshold of 5 mg per serving for disclosing the amount of caffeine on the label.

January 28, 1998: Dr. Hughes noted, in a letter to Dr. Michael Friedman, that FDA had not responded to the petition.

January 29, 1998: Elizabeth Campbell, for FDA, notified CSPI that FDA had not reached a decision within the first 180 days of receipt of the petition. She stated that the petition "raises complex issues" and that FDA was "reviewing critical studies on the major issues..."

August 7, 1998: Dr. Hughes again requested information on the status of the petition.

August 31, 1998: Elizabeth Campbell sent Dr. Hughes essentially the same letter she had sent CSPI six months earlier -- "raises complex issues" and "As soon as our evaluation is complete, we will notify you of the decision."

December 1, 1998: Sixteen months having passed without a decision, Dr. Hughes again wrote to Elizabeth Campbell requesting action.

April 30, 1999: Twenty months having passed, Dr. Hughes yet again wrote to Dr. Friedman requesting a status update.

July 14, 1999: Now two years since the original petition was filed, Dr. Hughes wrote again to Dr. Friedman requesting a status update.

August 5, 1999: Virginia Wilkening (Acting Director, Office of Food Labeling) wrote to Dr. Hughes, repeating the claim that our petition "raises a number of complex issues." Furthermore, she stated that our petition would be considered "among our program priorities for the calendar year 2000.
